M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

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FROM: Dianne Murphy, MD
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Office of the Commissioner

SUBJECT: Overview of the November 16-17, 2005 Meeting of the Pediatric Advisory Committee (PAC)

TO: Members of the Pediatric Advisory Committee

We look forward to seeing you in November and want to thank you for participating in the upcoming Pediatric Advisory Committee meetings on November 16-17, 2005. Attached you will find some background information and an overview of the agenda for these two days.

The Pediatric Advisory Committee (PAC) will meet on November 16th and 17th, 2005 to discuss the scientific and ethical issues incumbent in the development of pediatric trials to assess the safety and efficacy of devices utilized to effect weight loss. From social, medical and economic perspectives, the topic of obesity and its secondary co morbidities is a national health issue of great importance. Although most efforts at weight reduction must initially concentrate on changing lifestyle activities which have contributed to this health problem, other interventions may be considered when successful weight loss has not been achieved and the child remains at risk for poor health outcomes secondary to obesity.

During the two day meeting, experts will be discussing the epidemiology of pediatric obesity and the implications of conservative and surgical interventions for the treatment. The PAC will be asked to assist us in developing a scientifically and ethically sound approach to implementation of pediatric trials by addressing issues concerning the selection of an appropriate pediatric patient population for clinical studies, trial design, efficacy endpoints, ethical concerns, and long-term safety and effectiveness assessments.

We are providing you with extensive information as background reading. We would particularly direct your attention to the articles on surgical interventions as fundamental to your understanding of the risks and benefits of the types of products that are being considered for pediatric trials. Attached you will also find the list of rather extensive questions we are asking the committee. Your reading of these questions prior to delving into the background material should assist you in your review.

We have included multiple references which specifically address surgery in the adolescent population. One of these articles by Inge et al ("A critical appraisal of evidence supporting a bariatric surgical approach to weight management in adolescents.") provides a summary of

surgical weight loss procedures which are commonly performed in the adult population as well as some preliminary results on adolescents at his center undergoing some of these procedures. Articles by Sugerman et al ("Bariatric surgery for severely obese adolescents"), Capella et al ("Bariatric Surgery in Adolescents). Is this the Best Age to Operate"), Dolan and Fielding ("A comparison of laparoscopic adjustable gastric banding in adolescents and adults" and "laparoscopic gastric banding in morbidly obese adolescents"), Stanford et al ("Laparoscopic Roux-en Y gastric by pass in morbidly obese adolescents"), and Abu-Abeid et al ("Bariatric surgery in adolescence"), provide further results for various surgical procedures in small groups of adolescent subjects with follow-up out several years. A second article by Inge ("A multidisciplinary approach to the adolescent bariatric surgical patient"), describes one childrens hospital's Weight Management Center designed to appropriately select and manage adolescent bariatric patients. Several other references published by the American Academy of Pediatrics in one volume of *Pediatrics* (2004; Volume 114) are provided in your package. These include commentaries regarding bariatric surgery for adolescents on behalf of the American Pediatric Surgical Association (Dr. B. Rodgers) and the American Society for Bariatric Surgery (Dr. A. Wittgrove) as well as a general statement paper discussing concerns and recommendations issued after a national conference on the issue (Inge et al).

In addition to references specifically dealing with surgery in adolescents, we have included several very general references regarding bariatric surgical procedures in the adult population. These include several meta-analyses of surgical treatments for obesity (Maggard et al, Montefore et al, Buchwald et al) and an economic evaluation of bariatric surgery (Salem et al).

By way of background, to date, FDA has approved only two medical devices for the treatment of obesity. Only one of these, the "Lap-BAND" by Inamed, is still marketed. This device, however, is FDA approved for use in patients age 18 or over. Over the past several years, FDA has seen a significant rise in the number of applications to perform clinical trials with devices for the treatment of obesity in the adult population. Because medical devices may impart a higher degree of effectiveness compared to drugs and a lower risk profile compared to standard bariatric surgeries, the Agency anticipates that many manufacturers and investigators may wish to evaluate devices in the pediatric population as well because of the rising prevalence of the disorder in this group. As the clinical trials performed to assess the safety and effectiveness of any product remain the cornerstones of FDA approval for high risk or novel devices, the design of such studies is critical. FDA is therefore attempting to act proactively and assemble an appropriate panel of experts to discuss the issues related to, and provide recommendations on the proper trial design for such studies in this vulnerable population.
The agency has experience in working with manufacturers and investigators in designing clinical trials for obesity devices in the adult population. These studies have traditionally been limited to the patient population which meets eligibility for bariatric surgery – namely those subjects with a Body Mass Index (BMI) $\geq$ 40 or a BMI 35-40 with the presence of at least one medical comorbidity (diabetes, hypertension, sleep apnea, etc.). Most studies require patients to have failed more conservative therapies such as diet and exercise. Where possible, depending on the mechanics of the device and/or the (implantation) procedure, FDA encourages sponsors to perform randomized controlled trials (RCT), using sham procedures or inactive devices as controls when appropriate. Particular attention is paid to ensuring that diet, exercise, and behavioral therapies are kept consistent between control and treatment groups. The Agency has

been working to determine the most appropriate duration for sham or active control but generally recommends at least 6 months and up to 12 months. Depending on the device and the indications sought by the manufacturer, the primary endpoint may be assessed anywhere from 6 to 12 months or more from the start of treatment. Regulatory authority allows FDA to require post-approval studies as a condition of approval for Class III (high risk or novel devices) and this provides a mechanism for obtaining longer-term follow-up and assessment of safety and effectiveness beyond what might appear in the pre-market approval application (e.g., 5 years). FDA has generally used "percent excess weight loss" (%EWL) as the primary endpoint although other secondary endpoints may include absolute changes in weight, reduction in co-morbidities, and changes in quality of life parameters.

The FDA relies on the knowledge, judgment, experience, and wisdom of scientists and practitioners who participate as advisors and consultants. We thank you for your time and effort, and we look forward to seeing you and hearing from you on November 16th -17th, 2005.